Adrenocortical Tumors

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SUMMARY

Hormonally active tumors of the adrenal cortex are either benign adenomas or adenocarcinomas. They may be located within the adrenal gland or as adrenal rests along the Wolffian tract. Hyperplastic cortical tissue without actual neoplastic formation is also capable of elaborating excessive cortical secretions.

At the present state of knowledge, any one or a combination of the following compounds may be elaborated in a given case: the electrolytic, glucogenic, androgenic, or estrogenic corticosteroids.

Whether or not Cushing's syndrome is primarily pituitary or adrenal in origin is still a matter of conjecture.

FOR all practical clinical purposes tumors of the adrenal cortex may be classified as benign adenomas or adenocarcinomas. Sarcomas are mentioned frequently in the older textbooks, but several pathologists have assured the author that, if they occur at all, they are extremely rare.[14, 17, 18] It is felt that earlier observers perhaps mistook hypernephromas, or so-called Grawitz's tumors of the kidney, for sarcomatous neoplasms and, because of the vacuolized cells in such tumors with a "striking resemblance" to those of the adrenal cortex, assumed that they arose from cortical tissue.[24] There is another type of cortical neoplasm which should be mentioned, namely, those originating in adrenal rests along the Wolffian tract. While rare, these extra-adrenal hypersecreting tumors produce much the same clinical picture as those in situ. Since a patient with such a finding has recently come under the author's observation, this aspect of the subject will be discussed briefly in this presentation.

As to size, cortical tumors may range from mere granules, in an otherwise normal-appearing stroma, to retroperitoneal tumors so large as to misplace the entire abdominal contents. Moore[22] stated that "the frequency of local hyperplasia and adenomas of the adrenal cortex is in indirect ratio to the exactness of the criteria and examination. Most adrenals contain some type of spherical mass—grossly demonstrated nodules are present in about 10 per cent of all adults." Goldzieher[8, 9] and Grollman[12, 13] independently have stated that adenomatous nodules ranging from the size of small nests of cells to tumors the size of a hen's egg are observed in approximately one-third of all autopsies regardless of age or sex. Commons and Callaway[5] in an attempt to correlate the incidence of hypertension and diabetes with adrenocortical pathologic changes, encountered 216 tumors larger than 3 mm. in diameter in 7,434 consecutive autopsies (2.86 per cent).

If all these data are correct, it may be inferred that approximately 30 per cent of all adrenocortical neoplasms are smaller than a pea. Most, if not all, of the larger tumors are adenocarcinomas. The size of the neoplasm is no index of its secretory ability. Growths no larger than a hazelnut have produced profound alterations in the body economy, while those weighing a pound or more, although secretory, may exert barely discernible bodily changes. In fact, very large neoplasms have been found to be secreting tumors only after extirpation and examination. Most of the cortical adenomas are globular or egg-shaped and well set off from the remaining adrenal tissue though without the help of a connective tissue capsule. They are sulfur yellow in color and often contain darker yellow or brownish pigmented areas. Microscopically the cells may be arranged as in the normal cortex with the glomerulosa in the periphery and the fasciculata toward the center or, for some unknown reason, this arrangement may be completely reversed. The cells are abundant in lipoids which microscopically appear as vacuolized areas under the influence of solvents. Adenocarcinomas are soft growths of yellowish color prone to necrosis and hemorrhage.[9, 22]

Both the benign adenomas and the adenocarcinomas may be further subdivided into secretory and non-secretory tumors. Since the non-secreting varieties produce no demonstrable endocrine changes, they will not be dealt with in this presentation, which concerns neoplasms, both benign and malignant, that pour into the circulation sufficiently abnormal quantities of hormone to alter the body economy in a number of well recognized ways. However, an encapsulated neoplasm, whether benign or malignant, is not essential to cortical hyperfunction. Simple hyperplasia can and frequently does produce excessive amounts of cortical secretion with readily recognizable clinical results. While the hyperplasia may be bilateral, it is not uncommon to find contralateral hypoplasia in both simple hypertrophy and neoplastic disease. The latter finding, unless previously recognized, is an extra hazard to operation. On rare occasions metastatic tumors of the adrenal glands have been known to destroy the glands bilaterally with resultant Addison's disease.[27] Adrenocortical insufficiency has also been reported in persons who primarily presented evidence of Cush-

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ing's syndrome and in patients with precocious puberty.[4, 8, 3]

Confusion still exists as to what constitutes the classical clinical picture as a result of overproduction of cortical secretion. This is understandable in view of the many and varied biochemical factors involved. Here it is perhaps not amiss to give a clinician's viewpoint of the over-all picture as it appears at present. For, to understand even the fundamentals of the highly individualized steroids elaborated by the adrenal cortex is to realize that there is no single clinical picture of cortical overactivity, but rather various combinations of signs and symptoms, some most bizarre and seemingly paradoxical, which by inference implicate not only selective types of oversecretion but certain cytological structures as well. It is not yet possible to predict the cellular structure of a given neoplasm from the clinical picture encountered. However, this may not be far distant, since there is some experimental evidence to show that the zona glomerulosa secretes desoxycorticosteroids, which regulate fluid and electrolytic balance, and the zona fasciculata secretes 11-oxycorticosteroids which are concerned with gluconeogenesis, resistance to stress and the physiological mechanism of antibody production.[11]

While 27 or more compounds have been isolated from the adrenal cortex in crystalline form, at present four or perhaps five form the basis for most, if not all, clinical studies.[29] All of these are known to have been elaborated in greater or lesser quantities and in various combinations by both benign and malignant tumors. They are:

The electrolytic corticoids — Desoxycorticosterone, affecting mainly the balance of sodium, potassium, chloride and indirectly water, the overproduction of which results in the retention of salt and water, the excessive excretion of potassium—edema, hypertension and congestive heart failure.

The glucogenic corticoids — 17-hydroxy-11-dehydrocorticosterone (Compound E or cortisone), 11-dehydrocorticosterone (Compound A), corticosterone (Compound B), and 17-hydroxycorticosterone (Compound F), the overproduction of which results in muscular weakness, osteoporosis, a failing glucose tolerance, edema, fat deposits in the face and abdomen, amenorrhea, purplish striae of the skin, lymphopenia and eosinopenia, and a negative nitrogen balance.

The androgenic corticoids—Androstenedione, 11-hydroxy-isoandrosterone, androsterone and 17-hydroxyprogesterone, the overproduction of which produces masculinization of the female, lowering of the voice, amenorrhea, hypertrophy of the clitoris, acne, hirsutism, and occasional baldness; sexual and somatic precocity in the male child and heterologous changes in the female child.

The estrogenic corticoids—Estrone and progesterone, the overproduction of which produces feminization of the male, impotence, gynecomastia; homologous sexual precocity in the female child.

It is quite likely that as the various chemical compounds and their effects upon the body economy are elucidated, this list will grow. It is also to be hoped that some day the effects may be organized into regular clinical syndromes easy of recognition both as to pattern and etiologic delineation. At present, however, attempts at specific clinical classification leave much to be desired. Even the nomenclature is confused. A case in point is the classification of Kenyon,[19] which is as good as any and much better than most. He recognizes (1) the adrenogenital syndrome, (2) Cushing's syndrome, (3) mixed types including features of the two previously mentioned types, (4) a type characterized by a single endocrine manifestation, and (5) a type producing feminization of the male or homologous sexual precocity of the female.

The so-called adrenogenital syndrome must be considered first in the light of severity or degree. Where does normal function end and abnormal function begin so far as cortical function is concerned? Constitutionality alone plays a large part in the production of body type, body and facial hair, and even aberrant carbohydrate utilization. Many women of Russian-Jewish ancestry, as well as those of Mediterranean origin resemble, in a modified but sometimes rather startling manner, women who have Cushing's disease. Is their tendency toward trunk obesity, thin extremities, cervical kyphosis, hairiness and frequent family history of diabetes the result of inherent functional adrenocortical hyperactivity, or is this picture merely the reflection of the genetic type? Not so long ago, as a consultant, the author observed a moderately overweight young woman with facial, thigh and some chest hirsutism, who was being demonstrated as a patient with adrenocortical disease necessitating surgical treatment. However, when the patient was asked about her sister and mother, she said, "Both of them have more body hair than I." Obviously they did not all have adrenocortical disease. Frequently, however, it appears that hirsutism is not present in the mothers of such hairy females and that the tendency is apparently handed down from the male side of the family. It should be borne in mind that constitutional factors rather than adrenocortical, ovarian and testicular disease enter into some problems of homologous precocious puberty.

Aside from the factor of constitutionality and that of degree, the frank adrenogenital syndrome manifests itself differently according to the age of onset. Pseudohermaphroditism is said to be the result of adrenocortical hyperfunction in prenatal life. Pseudohermaphroditism has been produced experimentally in the offspring of pregnant animals which have been subjected to the administration of large doses of hormone.[10, 15, 28] One can see no reason why excessive production of either androgenic or estrogenic compounds would not produce sexual reverses in human fetal life; however, genetic deformities uninfluenced by sex hormones are so common elsewhere in the body as to argue against such etiological emphasis. If the so-called adrenogenital syndrome manifests itself early in life, it will produce sexual and somatic precocity of the masculine

type in young boys and heterologous changes or masculinization of the female. In adult women, amenorrhea, hypertrophy of the clitoris, atrophy of the breasts, body and facial hirsutism with alopecia of the scalp occur in varying degrees and combinations, while in the adult male only excessive masculinization is apparent.

It is next to impossible to discuss adrenocortical neoplasms without touching upon the perennial controversy concerning the primary cause of Cushing's syndrome.[7] There are two schools of thought: (1) that which clings to the theory that the primary disease is to be found in the adenohypophysis, as Cushing himself intended it to be, and that the adrenocortical lesions so commonly encountered are secondary to demonstrable cytological changes in this small but important organ; and (2) that which holds that the adrenal cortex is primarily involved and that the small basophilic adenomas and hyalinization or Crooke changes[6] in the cytoplasm frequently demonstrated in the adenohypophysis are merely the results of excessive cortical secretion. Both schools comprise experienced and conscientious observers.[1, 20, 3, 16, 21]

The fact that small basophilic adenomas of the anterior pituitary were found to be present rather frequently in persons in whom there was no clinical evidence of Cushing's disease,[23] while a number of patients with practically every symptom described by Cushing were discovered to have adrenocortical tumors, or cortical hyperplasia with few if any demonstrable changes in the pituitary, turned the tide in favor of the adrenal theory. The most recent (at least in print) champion of Cushing's original theory is Sosman,[25] by virtue of the fact that two out of six patients who had received roentgen irradiation to the pituitary, under his direction, have remained well for six years and 16 years. One patient, after pronounced improvement, had a relapse and died five years later, while one is living and apparently responding to treatment. Although the author for several years has been leaning toward belief in the primary involvement of the adrenal cortex, it must be admitted that the recently demonstrated potency and far-reaching clinical effects of the adrenocorticotropic hormone have somewhat shaken that belief. If under certain circumstances the adenohypophysis can pour into the circulation large amounts of this compound (ACTH) over a considerable period, almost anything could happen, especially to its target organ, the adrenal cortex. An overstimulated, hyperactive adrenal cortex could easily do the rest.

Cushing's syndrome, as it was originally known, consisted of a group of well recognized symptoms as follows: There was rapidly developing obesity of the face and trunk with concomitant atrophy of the extremities, purplish striae of the abdomen and flanks, purpuric and acneform eruptions of the skin, polycythemia, hypertension and decalcification especially of the spine, with early kyphosis. In addition, every female with this disorder that the author has observed has had, in a greater or lesser degree, some symptoms of masculinization such as excess facial and body hair, and occasionally amenorrhea, enlargement of the clitoris, and breast atrophy. It would therefore be difficult to recognize a clear-cut picture of Cushing's syndrome devoid of any or all of the evidences of the adrenogenital syndrome. It is also interesting to note that the administration of adrenocorticotropic hormone over long periods to arthritic patients produced the same untoward symptoms as prolonged cortisone administration, namely, the classical features of adrenocortical overactivity indistinguishable from the symptoms produced by hypersecreting adrenocortical neoplasms. It should also be noted that female patients so treated developed a degree of hirsutism and acne.[26]

Every patient with a frank adrenogenital syndrome, or the so-called corticometabolic syndrome (Cushing's disease) demands careful study. While the diagnosis can usually be made without difficulty at the time the patient seeks medical aid, the primary cause is frequently obscure. The physician must ask himself if the offending disease lies in the pituitary, the adrenal cortex, the thymus, in adrenal rests along the Wolffian tract, or perhaps in the fourth ventricle of the brain. Much depends upon the physician's attitude and therapeutic approach. A general physical and pelvic examination is, of course, essential. Studies of the urinary corticoids, ideal in all such problems, are still limited to endowed medical schools and institutions. Roentgenograms of the sella avail nothing since basophilic adenomas, if present, are too small, except in very rare instances, to present roentgen evidence of the disorder. Roentgenograms of the chest are essential in all patients to rule out enlargement of the thymus or neoplastic disease in the mediastinum. Roentgenograms of the skull, pelvis, spine and long bones may or may not reveal demineralization. Retrograde or even intravenous pyelograms may reveal a misplaced kidney, or on occasion be sufficient to outline a large adrenal tumor. Perirenal air insufflations in the adrenal area are used diagnostically by some physicians, but the procedure is considered relatively uninformative and even dangerous by others.

The 24-hour excretion of urinary 17-ketosteroids is more or less an index of the androgenicity of the cortical neoplasm. Values are usually considerably increased in the presence of malignancy with the predominant clinical picture of the adrenogenital syndrome. Moderately high values are found in benign adenomas, adrenal rests and simple hyperplasia, while values may be normal or only slightly elevated in Cushing's disease where virilism is a minor factor. A new and simple color test for dehydroisoandrosterone, said to be of value in the diagnosis of adenocortical tumors, has recently been devised.[2] The author has not had opportunity to evaluate it.

Other laboratory values vary according to the type and concentration of the elaborated secretions. The serum cholesterol, while frequently elevated, may be normal. There is usually a poor glucose tolerance with frequently a frank diabetic curve and

glycosuria. The basal metabolic rate and protein-bound iodine are frequently elevated. There may, or may not, be retention of sodium and chloride with potassium excretion resulting in hypertension.

If the corticogenital or corticometabolic syndrome is present and the offending lesion is not apparent, primary exploration by the abdominal route should be carried out. This gives opportunity to palpate both adrenals and to aid in the retroperitoneal extirpation of the adrenocortical neoplasm or hyperplasia, if and when discovered. In the female it also affords opportunity to see and palpate the ovaries and adjacent structures for adrenocortical rests and other virilizing neoplasms.

In addition to routine measures, patients undergoing cortical extirpation should be prepared by the administration of liberal quantities of the cortical hormone the day before, during and immediately following the operation. Large quantities of hormone are occasionally necessary for several days postoperatively to keep the patient from rapid collapse and death. Successful extirpation of the neoplasm results in amelioration or complete elimination of the entire symptom complex over a period of time.

CASE REPORTS

A girl 13½ years of age was referred because of a recent growth of hair on the face and sides of the neck. Although the patient came from a "very hairy family," her mother felt that this type and distribution of hair was probably not normal. The patient began to mature at 11 years of age—the breasts filled out to a moderate degree, and pubic and axillary hair appeared. She had never menstruated. When she was about 12½ years of age her voice began to change and to break on occasion like that of any adolescent boy. The psyche was preadolescent but entirely feminine. The patient was otherwise well.

Well developed and with normal feminine configuration, the patient was 65.5 inches in height, and weighed 127.7 pounds. There was abundant head hair, slight hairiness of the face and neck, and a male pubic escutcheon. The abdomen and legs had been shaved. Upon pelvic examination the vaginal introitus was noted to be small, but a sound could be inserted for approximately 3 inches. The clitoris was large and hooded, the labia were small. A small nodule which was believed to be an undeveloped uterus was noted in a rectal examination.

The basal metabolic rates were -21, -26. The blood cell count was normal except for moderate eosinophilia. There were no abnormalities in the urine and the blood values for cholesterol, protein-bound iodine, glucose tolerance, and icteric index were all within normal limits. Intravenous urograms and x-ray films of the skull were negative. The 17-ketosteroid excretion was 26.6 mg. in 24 hours (normal values for females, 8 to 13 mg.).

At first the patient was considered as having a benign adrenogenital syndrome and 5 mg. daily of stilbestrol was administered. In spite of gradually increasing the dosage up to 20 mg. daily, hirsutism became rapidly more pronounced. No withdrawal bleeding was produced. While large doses of stilbestrol were being given, the 24-hour 17-ketosteroid excretion at first dropped to around 10 mg., but approximately eight months after the initial examination, the values had risen to 42.6 mg. The face hirsutism had become increasingly embarrassing and exploratory operation was decided upon.

At laparotomy, performed about ten months after the patient first came under observation, the uterus was noted to be very small and undeveloped. The ovaries were small and sclerotic and the left ovary contained a cyst at the upper pole approximately 2 cm. in diameter. The cystic mass was excised and wedge-shaped biopsies were taken from both ovaries. The mass contained a mushy, yellowish material, similar to but not exactly like the material found in corpus luteum cysts. On palpation both adrenal glands appeared to be moderately hypertrophic. The postoperative course was uneventful.

The pathological report was as follows:

A mass 8 mm. in diameter removed from the left gonad revealed two blue-brown areas of tissue with attached capsule, each of which measured up to 2 cm. in greatest dimension. On section these masses were observed to consist of a group of clear cells resembling luteal cells but more like adrenocortical tissue containing a dusting of dark brown pigment.

Special stains were made to detect the presence of a hormone according to the method of Camber.* Fresh adrenal cortex was used as control. Positive pink-red stain for the presence of adrenocortical hormone was found in abundance in the ovarian tumor cells.

The wedges taken from the sclerotic but otherwise normal-appearing gonad sites contained numerous ova within a single layer zone of granulosa cells. None of them were stimulated to the formation of follicles or germinal hillocks. The findings were identical with those in normal prepubertal ovarian cortex.

The final diagnosis was adrenal cortex rest of left ovary.

Follow-up: The patient began menstruating two months after operation. The breasts gradually became larger, the uterus began to enlarge, the hair on the face, chest and arms gradually became finer and thinner, and the skin became soft and smooth. At the last observation, seven months after operation, the patient stated that she had been menstruating regularly. The cycle took 28 to 34 days with a four- to five-day period of rather scanty menses. The vaginal epithelial cells were well cornified and occurred in small sheets. The general configuration, psyche, and hair distribution were becoming more and more mature and feminine although the voice remained low.

* * *

A white married woman 36 years of age complained of a rapid gain in weight, from 128 pounds to 199 pounds since the birth of her last child, three years previously. Other complaints were of weakness, especially of the lower extremities, irregular menstruation, and hemorrhagic spots over the body.

Very obese, the patient was 63 inches in height, and weighed 189 pounds. Most of the weight was limited to the trunk; the arms and legs were relatively thin. There was also the characteristic kyphosis of the cervical spine so commonly seen in Cushing's syndrome. There was slight hirsutism of the face, but the distribution of hair over the body was otherwise normal. The blood pressure was 170 mm. of mercury systolic and 90 mm. diastolic. The heart appeared to be moderately enlarged in all diameters but the sounds were forceful and of good quality with a regular rhythm. Dark-bluish striae covered the abdomen. The liver appeared to be enlarged, the lower edge extending from 5 to 6 cm. below the costal margin on the right. It was not tender, and no nodules could be felt. Neither kidney could be palpated. Roentgenograms of the skull revealed a small, bridged sella turcica. Basal metabolic rates were zero. The urine, blood cell count, hemoglobin content, sedimentation rate and glucose tolerance were essentially normal. Cholesterol values

* Camber, B.: Histochemical demonstration of ketosteroids in the adrenal cortex, Nature, 163:285-286, Feb. 19, 1949.

were 277 mg. per 100 cc. of blood. Twenty-four hour excretion of urinary 17-ketosteroid was 5 mg. on one occasion and when repeated before operation was 2.6 mg. Air insufflation of the perirenal area was considered, but because of abdominal obesity and the advantage of more complete abdominal exploration, laparotomy was performed about eight months after the initial examination. The uterus was normal in size, firm in consistency and of regular contour. The right ovary was adherent to the posterior surface of the broad ligament. The liver was moderately enlarged, the gallbladder and spleen normal, the kidneys small. On the right adrenal gland was a walnut-sized mass which seemed to be circumscribed and much firmer than the surrounding tissue. The left adrenal gland was normal in size and consistency. The abdominal incision was closed without drainage and the tumor removed through a right subcostal incision.

Following the operation the patient went into shock and, in addition to routine measures, a large amount of adrenal cortex substitution was necessary. In all, 420 cc. of aqueous cortical extract and 16 cc. of lipo-adrenal cortex extract were administered in five days during the postoperative crisis.*

The pathological report was as follows:

The right adrenal gland contained a bright orange cortical tumor measuring 3.5 x 2.5 x 1.8 cm. At the edge of the adenoma there was evidence of dissection, and other fragments of this cortical tumor were submitted separately. There appeared to be compression of the subjacent adrenal gland, and section through the adrenal gland tissue revealed a central portion that was gray in color. Upon examination of sections, the tumor was noted to be rather uniformly bright yellow-orange in color, with focal areas of gray-tan in the central portion. The second portion of the specimen consisted of gray-tan lymph nodal structure obtained from the para-aortic area. The third portion consisted of fatty tissue also obtained from the para-aortic area.

Microscopic examination of sections through the compressed normal adrenal gland tissue including division of the cortex and medulla revealed these structures to appear essentially unchanged except for the fact that some of the adrenocortical cells appeared to contain a little less than the normal amount of fat. Lymphoid and fatty tissue without evidence of malignancy was noted in examination of sections through the second and third portions of the specimen.

Diagnosis: Benign adrenocortical adenoma, right adrenal gland.

Follow-up: The patient began losing weight shortly after leaving the hospital and in all lost approximately 30 pounds. Menstruation began two months after the operation. Many of the abdominal striae faded and most of the facial hair disappeared. The blood pressure was 130 mm. of mercury systolic and 90 mm. diastolic. The patient tired easily and was extremely sensitive to cold.

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